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(21) International Application Number: PCT/EP92/01425 (22) International Filing Date: 24 June 1992 (24.06.92) (30) Priority data: P 41 20 760.2 24 June 1991 (24.06.91) DE (71) Applicant (for all designated States except US): MINNESOTA MINING AND MANUFACTURING COMPANY [US/US]; P.O. Box 33427, Saint Paul, MN 55133-3427 (US). (72) Inventors; and (75) Inventors/Applicants (for US only) : ZERBE, Horst [DE/DE]; Wilhelm-Busch-Str. 4, D-4282 Velen (DE). KREUTER, Jörg [DE/DE]; Georg-August-Zinn-Str. 13, D-6380 Bad Homburg (DE). ZIMMER, Annette [DE/DE]; Eleonore-Sterling-Str. 53, D-6000 Frankfurt (DE).		(74) Agent: VOSSIUS & PARTNER; Siebertstrasse 4, P.O. Box 86 07 67, D-8000 München 86 (DE). (81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: CARRIER SYSTEMS FOR DRUGS (57) Abstract The invention relates to carrier systems for drugs, their preparation and their use. The carrier systems according to the invention exhibit spherical particles with a diameter of less than 1 µm, optionally in combination with an appropriate bioadhesive polymer. The carrier systems have an improved bioadhesiveness and a high loadability with drugs and are able to provide a stable, pharmaceutically active concentration of drugs at the site of action over a longer period of time.		

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Carrier Systems for Drugs

The invention relates to carrier systems for drugs, their preparation and their use.

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The therapeutic effect of a drug inter alia is dependent on the concentration of the drug at the site of action for a desired period of time. On grounds of this dependence, factors such as distribution, dilution, excretion, absorption or biotransformation play an important role for the therapeutic effect of a drug. All of these factors must

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be taken into account in particular when formulating a drug.

One possibility of improving the therapeutic effect of a drug is to use carrier systems such as viscous solutions, ointments, bioadhesive polymers or spherical particles [1-9]. U.S. Patent 4,617,186 discloses, for instance, a cationic polymer ("GAFQUAT-234") that possesses bioadhesive properties and can be used as a carrier system for drugs for the treatment of eye diseases; Moreover, this polymer is also said to be able to bind spherical particles of albumin, which also represent carrier systems for drugs. The complexes of the polymer and the carrier system are said to be bioadhesive and to retard the drug release but no comparative data vis-à-vis the polymer alone are given in support of this statement. Furthermore, in particular cationic polymers are to be considered problematic because of their toxicological properties.

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1 Solutions, ointments and specific polymers distinguish
themselves in particular by their high capacity for drug
incorporation. Solutions exhibit considerable disadvantages
5 over ointments and polymers due to the fast dilution,
excretion and biotransformation of the drug, which entails
that the drug concentration drops rapidly below the
pharmaceutically active level at the site of action.
Ointments, when applied to the eye, lead for example to a
10 severe impairment of vision. A disadvantage of the known
spherical particles as carrier systems is above all the low
drug incorporation capacity, which may also entail too low a
concentration of a drug at the site of action. Another
disadvantage of known spherical particles is their low
15 bioadhesiveness, which leads to a rapid excretion of these
particles.

The problem underlying the invention is the provision of
carrier systems for drugs, which remain for a prolonged time
at the site of application by an improved bioadhesiveness,
20 exhibit a high loadability with drugs and provide a stable
concentration of drugs at the site of action over the
desired period of time, in order to improve the therapeutic
effect of drugs.

25 This problem is solved by the features of the claims.

In a first embodiment, the carrier system of the present
invention exhibits spherical particles with a diameter of
less than 1 μm , preferably less than 500 nm, most preferably
30 100 nm to 300 nm. In the following, such particles will also
be called nanoparticles. By "particle size" the mean
diameter of the particles is meant.

Nanoparticles as a carrier system for drugs display various
35 advantages over the known microparticles with a diameter of
at least 1 μm . The nanoparticles can be better distributed
in a liquid since no significant sedimentation of the

1 particles takes place. As a rule, no surfactants need to be
added in order to disperse the particles. The nanoparticles
can also be used as drug vehicles in inhalation aerosols.
5 The nanoparticles have a larger specific surface and thus a
higher incorporation capacity. Thus they enable an enhanced
effect of the drug when used as a carrier system.

10 The spherical particles of the present invention preferably
contain at least one synthetic, semi-synthetic and/or
natural biopolymer, most preferably a polypeptide such as
albumin or gelatine. Functional groups of the biopolymer
such as $-NH_2$, $-CO_2H$, $-COH$ or $-SH$ permit covalent bonds with a
multitude of drugs.

15 The spherical particles according to the present invention
can incorporate both hydrophobic and hydrophilic drugs,
wherein the loadability generally depends on the drug, e.g.
15 % by weight of pilocarpine with respect to the spherical
particles, and the weight ratio of particle to drug can be
20 up to 1:1.

The spherical particles are non-toxic, biodegradable by
lysosomal enzymes, biocompatible, physically and chemically
stable and do not possess any relevant antigenic properties.
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Furthermore, the spherical particles of the invention have a
controllable drug release rate and are rapidly excreted.

30 Another embodiment of the carrier system according to the
present invention comprises spherical particles with a
diameter of at least 1 nm and less than 1 mm, i.e.
microparticles and nanoparticles, in combination with at
least one bioadhesive polymer such as pectins
(polygalacturonic acid), mucopolysaccharides (hyaluronic
35 acid, mucin) or non-toxic lectines. In the following, such a
carrier system will also be called particle/polymer carrier
system. Not all bioadhesive polymers known in the state of

1 the art necessarily entail a synergetic effect when used as
a carrier system in connection with spherical particles. The
use of polysaccharides, polyacrylates, alginates, polyvinyl
alcohol, polyethylene glycol, polyvinyl pyrrolidone and
5 lectines is preferred. Most preferred is the use of methyl
cellulose 400, sodium carboxymethyl cellulose, Carbopol®
941, hydroxypropyl methyl cellulose, hyaluronic acid, sodium
alginate MV, mucin and polycarbophil.

10 The bioadhesive polymers preferably have a viscosity of 4×10^{-3} to 100×10^{-3} Pas, the retarded drug release being
improved at a higher viscosity. Generally, a higher
viscosity of the polymers is advantageous. However, the
viscosity increase is restricted for practical reasons, for
15 example in the application to the eye. The weight ratio of
spherical particles to bioadhesive polymer inter alia is
dependent on the used polymer and can for instance be 2:1 to
1:2.

20 The advantages of particle/polymer carrier systems for drugs
over pure particle carrier systems are on the one hand an
increased incorporation capacity due to an increased
adsorption of the drug molecules and on the other hand a
lower required dose of the drug due to a prolonged effect of
25 the drug and thus less discomfort for the patient.

The bioadhesive effect of the polymers is probably due to an
intermolecular interaction, such as ionic interactions, Van
der Waals interactions, hydrogen bonds or molecular
30 entanglement of the polymer with surface components, such as
proteins or lipids, of mucous surfaces, or to other physical
phenomena, such as capillary action or viscosity.

35 A further aspect of the invention is a composition that
contains at least one of the aforementioned carrier systems,
a drug and optionally a further pharmaceutically acceptable
carrier or diluent.

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The weight ration of drug to carrier system is conventionally in the range of 100:1 to 1:1000, preferably 10:1 to 1:10 and most preferably 2:1 to 1:2 or 2:1 to 1:1.

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The preparation of the spherical particles according to the invention can be carried out by several alternative methods. Suitable methods are the desolvation of the biopolymer used as starting material by dehydrating compounds, such as alcohols or sodium/ammonium sulfate, the thermal denaturation of the biopolymer by heating to 95°C to 195°C, the reaction of the biopolymer with a coupling reagent and/or the reaction of the biopolymer with a compound ("hardener") having two or more functional groups, such as glutaraldehyde.

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The resultant spherical particles are suspended in a concentration of up to 10 % (w/v) in an appropriate solvent, for instance water.

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The size as well as the diameter of the spherical particles can be optimized by varying appropriate parameters, such as temperature, concentration of the biopolymer, concentration of the hardener or selection of the dehydrating agent (e.g. absolute alcohol instead of salts), or by further appropriate method steps, such as ultrasonication of the particles. Furthermore, the spherical particles can also be chromatographically purified over a suitable column (gel filtration).

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A preferred method for the preparation of the spherical particles comprises the addition of 100 % ethanol to a solution of 0.25 to 1.5 % (w/v) of a polypeptide, preferably less than 1.25 % (w/v) of the polypeptide, in distilled water, the mixing ratio of ethanol:polypeptide solution being > 1:1 to 2:1. After the onset of the polypeptide desolvation, 0.01 to 1 % (v/v) of 25 % glutaraldehyde are

1 added to said mixture. After about 1 hour, a corresponding
amount of a 12 % (w/v) sodium metabisulfite solution is
added in order to decompose the excess glutaraldehyde. After
about 3 hours, the ethanol is evaporated and the obtained
5 particle suspension column-chromatographically purified. The
particle-containing fraction is subsequently lyophilized
while glucose is added.

When preparing the spherical particles, intermolecular and
10 intramolecular bonds, such as covalent bonds, or
interactions, such as hydrophobic interaction, with
particular functional groups of the biopolymer, such as $-NH_2$,
 $-CO_2H$, $-COH$, $-SH$ or phenyl groups, are produced.

15 The preparation of the particle/polymer carrier systems
according to the invention comprises mixing at least one
appropriate bioadhesive polymer with a suspension of
spherical particles. Said spherical particles can be
produced according to the aforementioned inventive method or
20 according to methods known in the state of the art [10-12].

The preparation of the composition of a drug and a carrier
system according to the invention comprises the adsorption
or loading of a drug into or onto the spherical particle and
25 can be performed either simultaneously with the preparation
of the carrier system by the addition of an appropriate drug
solution or sequentially by the addition of a suspension of
spherical particles to an appropriate drug solution.
Furthermore, the preparation optionally comprises the
30 addition of 0.1 to 2 % of a surfactant.

The loading process of the carrier system with a drug is
probably based on a bond of the drug molecules with the
carrier system, in which said molecules are complexed by
35 intermolecular interactions, such as hydrogen bonds, with
specific groups of the biopolymer, such as $-NH_2$, $-OH$, $-COOH$
or $-SH$.

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The carrier system according to the invention can incorporate a multitude of drugs, such as antiasthmatics, analgetics, antitussiva, bronchodilators, narcotics, mucolytics, antibacterials, antifungals, antituberculosis agents, steroids, antitumor agents, parasymphomimetics, fibrinolytics, immunosuppressives etc.

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The drug-loaded carrier systems according to the present invention can be administered intraarticularly, cutaneously, subcutaneously, intramuscularly, intravenously, intraarterially, intravaginally, rectally, orally, nasally and ocularly. The drug-loaded particle/polymer carrier systems are preferably applied onto mucous surfaces of mammals, including humans.

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A preferred application comprises the formulation of a composition of carrier systems and drugs, which are administered for the treatment of eye diseases, such as glaucoma, inflammations, infections and allergic reactions.

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When selecting the particle size, the intended application plays an important role. For example, carrier systems that contain spherical particles with a diameter of more than 25 μm are not suitable for the application to the eye because of the pain sensation. The lowest limit for the particle size is essentially not restricted by the application, however, it is difficult to produce particles with a diameter of $< 10 \text{ nm}$. Furthermore, particles with a diameter of $< 10 \text{ nm}$ lead to a rapid accumulation at the eye or to an exhalation in the application as an inhalation aerosol.

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In the following the invention will be explained in more detail by means of the drawings.

1 Figure 1 shows a diagram of the miotic activity of a
pilocarpine composition containing albumin nanoparticles
against time, with a 2 % pilocarpine solution as a
reference.

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Figure 2 shows a diagram of the miotic activity of a
nanoparticle/mucin/pilocarpine composition (weight ratio
1:1.25:1) against time, with a mucin/ pilocarpine
composition (weight ratio 1.25:1) as a reference.

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Figures 3 and 4 show a diagram of the intraocular pressure
(mm Hg) of a 2 % pilocarpine solution, a microparticle/
pilocarpine composition and a nanoparticle/mucin/pilocarpine
composition against time, wherein the temporal change of the
pressure without the addition of a drug is defined as a
baseline.

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The following examples illustrate the invention.

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Example 1: Albumin Nanoparticle/Pilocarpine Composition

(A) The Preparation of the Albumin Nanoparticles

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500 mg bovine serum albumin are dissolved in 40 ml of
distilled water and 100 % ethanol is slowly dropped in
while stirring is maintained. After the addition of
about 60 ml of 100% ethanol, the desolvation of the
bovine serum albumin can be observed by a slight blue
shimmer of the mixture. 0.1 ml of 25 % glutaraldehyde is
added to the mixture during stirring and subsequently
agitation is continued for about 3 hours. The excess
glutaraldehyde is decomposed by the addition of 1 ml of
12 % sodium metabisulfite solution. After further 3
hours of agitation, the ethanol is evaporated under
vacuum. The remainder is chromatographically purified
over a Sephacryl S-1000 column (Pharmacia). The obtained
particle suspension is lyophilized by the addition of

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1 glucose for about 16 hours. The particle diameter in
this method is 100 to 200 nm (measured with particle
measuring device BI-90, Brook Haven Instruments).

5 (B) Pilocarpine-Loading

20 mg/ml of the nanoparticles are added to a 2 %
pilocarpine nitrate solution (containing 1.2 % of
pluronic F 68, 1 % of sodium sulfate, phosphate-
10 buffered, pH 7) and the mixture is equilibrated to reach
an equilibrium while stirring. The mixture is then
filtrated by ultrafiltration and the amount of the free
pilocarpine is spectroscopically determined. The amount
of incorporated pilocarpine is 11.8 mg/100 mg carrier.
15 The amount of incorporated pilocarpine in the case of
particles with a diameter of 1-2 μm is only 5.8 mg/100
mg carrier.

20 (C) Determination of the Miotic Activity

The determination of the miotic activity is carried out
with male albino New Zealand rabbits. Each of the
experiments is performed with 5 rabbits and a dose of 50
 μl of nanoparticle/pilocarpine composition. The measure-
25 ments of the pupillary diameter are carried out under
constant light conditions with a micrometer that is held
at a fixed distance from the rabbit's eyes. The results
are graphically depicted in Figure 1. The duration of
effect of pilocarpine increases by up to 14 %, with the
30 half-life ($t_{1/2}$) being prolonged by up to 19 %. The
half-life is defined as the moment at which the miosis
exhibits half of its maximum value.

1 Example 2: Nanoparticle/Mucin/Pilocarpine Composition

 (A) The Preparation of the Bovine Serum Albumin/Mucin
 Composition

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 The nanoparticles as described in example 1(A) are
 suspended in an appropriate buffer, pH 7, and 2.5 % or
 4.5 % of mucin are added, solutions with viscosities of
 $4-7 \times 10^{-3}$ Pas or $13-17 \times 10^{-3}$ Pas, respectively, being
10 obtained.

 (B) Pilocarpine-Loading

 The nanoparticle composition is suspended in a 2 %
15 pilocarpine solution as described in example 1(B), and
 subsequently mucin is added.

 (C) Determination of the Miotic Activity

20 The determination of the miotic activity is carried out
 as described in example 1(C). The results are
 graphically depicted in Figure 2 and in Table I. The
 effect of pilocarpine (Pilo.) is prolonged by up to 90
 min (duration of effect [min]), the half-life ($t_{1/2}$)
25 being prolonged by up to 62 %. The effect of pilocarpine
 is directly proportional to the miosis.

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TABLE I

Carrier System	Measuring time ^{a)} [min]	I max ^{b)} [mm]	Duration [min]	AUC ^{c)}	t1/2 [min]
Mucin 2.5% Micro- particle 2% Pilo. 2%	30	2.66	300	386.40	130
Mucin 2.5% Pilo. 2% Reference	30	2.40	210	230.74	97
Mucin 2.5% Nano- particle 2% Pilo. 2%	15	4.26	300	631.95	155
Mucin 2.5% Pilo. 2% Reference	30	3.68	210	394.53	122
Mucin 4.5% Micro- particle 4% Pilo. 2%	30	3.08	300	425.25	135
Mucin 4.5% Nano- particle 4% Pilo. 2%	30	4.15	300	629.74	157

a) moment of maximum pupillary contraction

b) maximum pupillary contraction

c) "area under the curve" (integral of the time-of-effect curve)

(D) Determination of the Intraocular Pressure (Betamethasone Model)

0.8 ml of betamethasone is subconjunctivally injected into the right eye of 13 male albino New Zealand rabbits. The injections are performed weekly over a period of 3 weeks. After three weeks, the ocular hypertension becomes stable. 50 μ l of a particle/pilocarpine composition or a particle/mucin/pilocarpine composition are subsequently instilled into the conjunctival sac and then the intraocular pressure is measured. The results are graphically depicted in Figures 3 and 4 as well as in Table II. The time-of-

effect curve and thus the bioavailability of pilocarpine increase by up to 220 % with respect to a 2 % pilocarpine solution. The bioavailability is defined as the fraction of a drug that is determined with respect to the dose in the measuring compartment, with a direct correlation existing between the concentration and the effect of the drug. The effect of pilocarpine is prolonged by up to 100 % (duration of effect [h]).

TABLE II

Preparation	Duration [h]	AUC [cm ²]	Bioavailability [%]
Pilocarpine 2% Reference	3.5	19.03	100.0
Pilocarpine 2% Nanoparticle 2%	5.5	20.28	205.26
Mucin 4.5% Micro- particle 4% Pilo. 2%	7.0	31.53	319.12

Example 3: Loading of Hydrocortisone onto Nanoparticles

Nanoparticles as described in example 1(A) are suspended in water and added to a saturated solution of hydrocortisone in ethanol (13.33 mg/ml). The mixture is ultrafiltrated through a 10 nm filter and the hydrocortisone-adsorbed nanoparticles are retained. The hydrocortisone contained in the filtrate is subsequently spectroscopically determined at 247 nm. The nanoparticles contain 6.81 % of hydrocortisone. The amount of hydrocortisone loaded onto particles with a diameter of 0.8 to 1.5 μ m is 4.02 %.

1 Literature:

- [1] U.S. Patent 4,617,186;
- [2] Ribinson, J.R. et al. (1984), 231-236 in: Recent
5 advances in glaucoma, eds. Ticho et al., Elsevier
Science Publishers B.V.;
- [3] Ch'ng, H.S. et al. (1985), J.Pharm. Science 74 (4),
399-405;
- [4] Park, K. et al. (1984), Int. J. Pharmaceutics 19, 107-
127;
- 10 [5] Langer, M.A. et al. (1985), J.Pharm. Science 74 (4),
406-411;
- [6] Wood, R.W. et al. (1985), Int. J. Pharmaceutics 23,
175-183;
- [7] U.S. Patent 4,671,954;
- 15 [8] U.S. Patent 4,582,719;
- [9] Lehr et al. (1989), Proceed. Intern. Symp. Control.
Rel. Bioact. Mater., 16, 418-419;
- [10] U.S. Patent 4,107,288;
- [11] Knop, G et al. (1974), Nuklearmedizinisches Symposium
20 in Reinhardsbrunn DDR, 315-319;
- [12] Widder, K. et al. (1979), J. Pharm. Sci. 68, 79- 82.

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C L A I M S

- 5 1. A carrier system for drugs, said carrier system comprising spherical particles with a diameter of less than 1 μm .
2. The carrier system according to claim 1, wherein the spherical particles have a diameter of less than 500 nm.
- 10 3. The carrier system according to claim 1, wherein the spherical particles have a diameter of 100 to 300 nm.
- 15 4. A carrier system for drugs, said carrier system comprising spherical particles with a diameter of at least 1 nm and less than 1 mm, and at least one bioadhesive polymer.
- 20 5. The carrier system according to claim 4, wherein the bioadhesive polymer has a viscosity of 4×10^{-3} to 100×10^{-3} Pas.
6. The carrier system according to claim 4 or 5, wherein the bioadhesive polymer is neutral or anionic.
- 25 7. The carrier system according to any of claims 4 to 6, wherein the bioadhesive polymer is selected from the group consisting of polysaccharide, polyacrylate, alginate, polyvinyl alcohol, polyethylene glycol, polyvinyl pyrrolidone and lectine.
- 30 8. The carrier system according to any of claims 4 to 7, wherein the bioadhesive polymer is selected from the group consisting of methyl cellulose 400, sodium carboxymethyl cellulose, Carbopol[®] 941, hydroxypropyl methyl cellulose, hyaluronic acid, sodium alginate MV, mucin and polycarbophil.
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9. The carrier system according to any of claims 1 to 8,
wherein the spherical particles consist of at least one
5 synthetic, semi-synthetic or natural biopolymer.
10. The carrier system according to claim 9, wherein the
biopolymer is the protein albumin.
- 10 11. A composition consisting of a carrier system according
to any of claims 1 to 10 and a drug.
12. The composition according to claim 11, wherein the
weight ratio of drug to carrier system is in the range
15 of 100:1 to 1:100.
13. A method for preparing a carrier system according to any
of claims 1 to 3, said method comprising at least one of
the following method steps in the preparation of the
20 spherical particles:
(A) desolvation of a synthetic, semi-synthetic or
natural biopolymer,
(B) thermal denaturation of a synthetic, semi-synthetic
or natural biopolymer,
25 (C) reaction of a synthetic, semi-synthetic or natural
biopolymer with a coupling reagent, and/or
(D) reaction of a synthetic, semi-synthetic or natural
biopolymer with a compound that contains two or more
functional groups.
- 30 14. The method according to claim 13, wherein the compound
in step (D) is glutaraldehyde.
15. A method for preparing a carrier system according to any
35 of claims 4 to 10, said method comprising at least one
of the method steps (A) to (D) according to claim 13,
and the further step of mixing the formed spherical
particles with at least one bioadhesive polymer.

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16. A method for preparing a composition according to claim 11 or 12, said method comprising the step of adding an appropriate drug solution

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(A) during the preparation of the carrier system according to the method of any of claims 13 to 15, and/or

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(B) after the preparation of the carrier system according to the method of any of claims 13 to 15.

17. A method of treatment comprising administering to a patient in need of such a treatment a composition according to claim 11 or 12.

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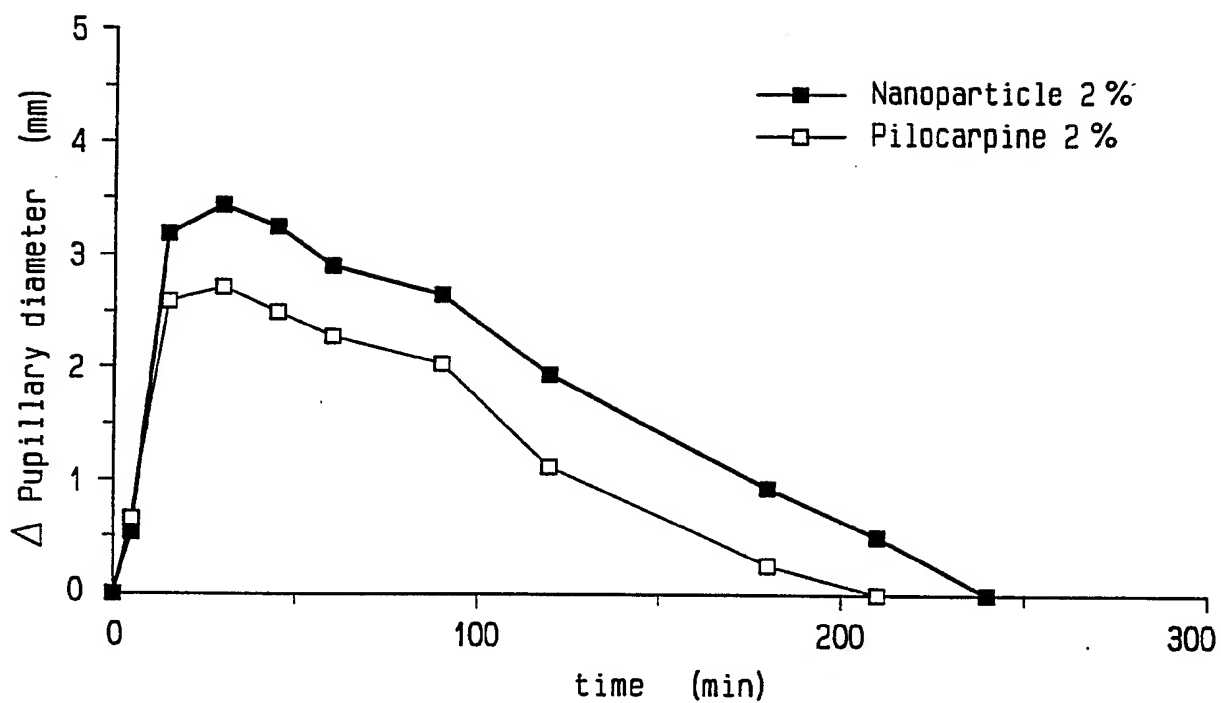


Fig. 1

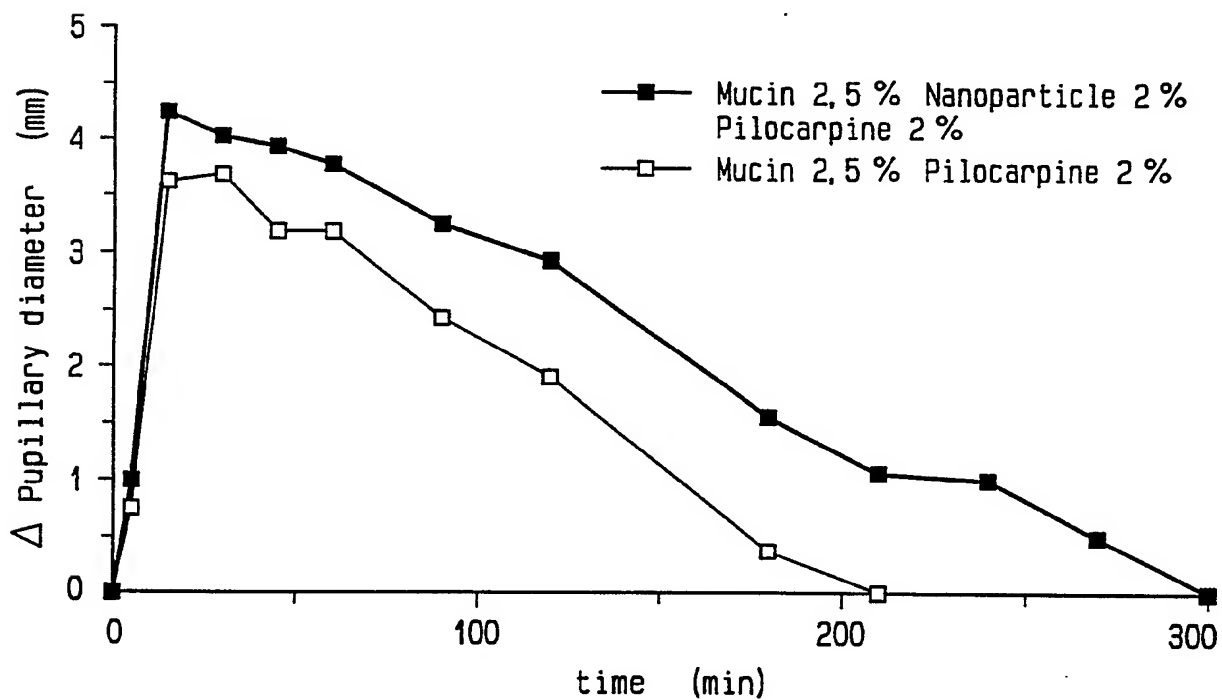


Fig. 2

SUBSTITUTE SHEET

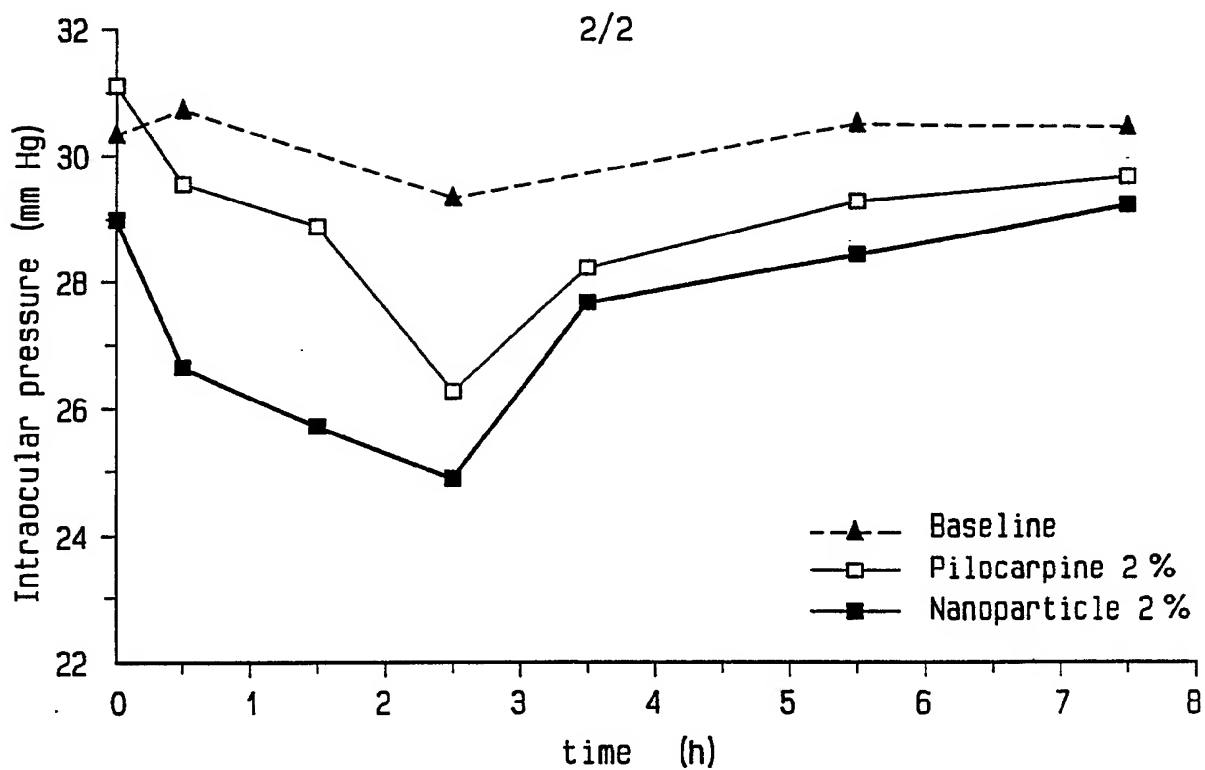


Fig. 3

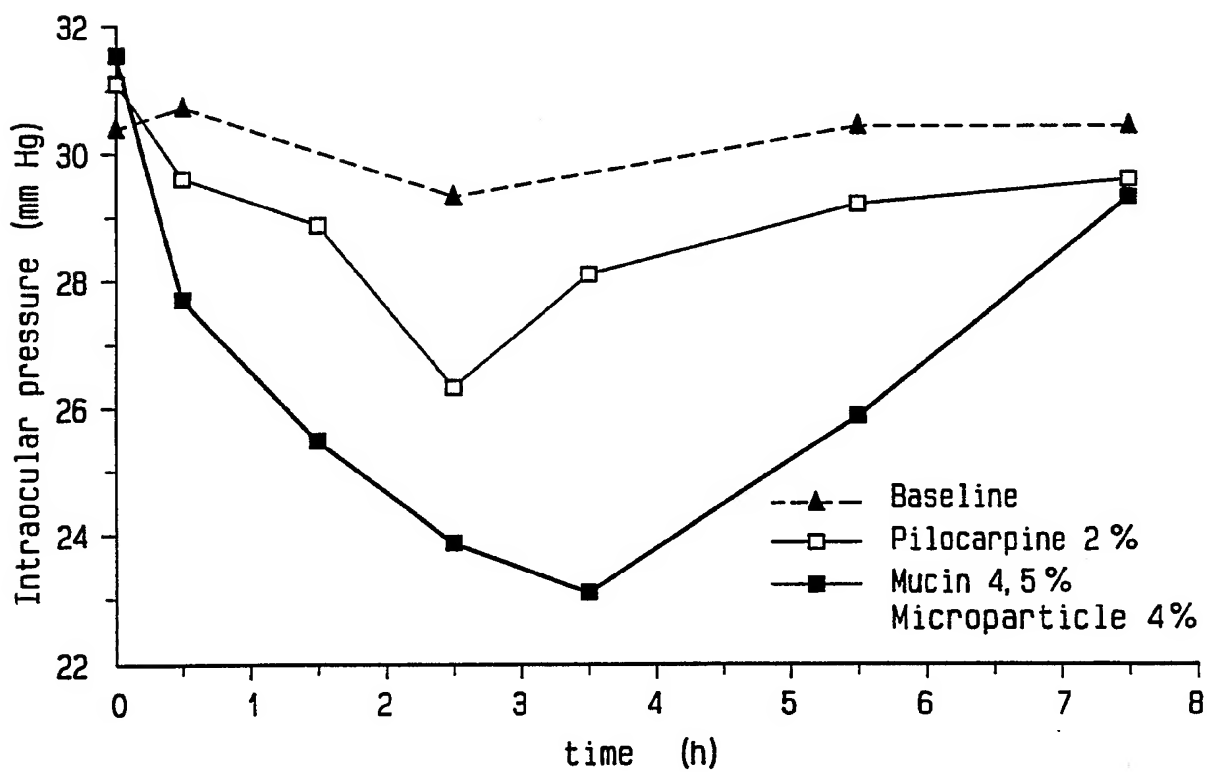



Fig. 4

SUBSTITUTE SHEET

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 92/01425

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 A61K9/51; A61K9/16		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	GB,A,1 516 348 (PHARMACEUTICAL SOCIETY OF VICTORIA) 5 July 1978 see the whole document ---	1-4, 9-11, 13-14
X	WO,A,9 004 963 (DANBIOSYST UK LIMITED) 17 May 1990 see claims 1-5,8 see page 3, line 11 - line 18 see page 8, line 20 - page 9, line 3 see page 15, line 5 - line 15 ---	4,9-16
P,X	EP,A,0 486 959 (VECTORPHARMA INTERNATIONAL S.P.A.) 27 May 1992 see claims 1-3 see page 4, line 20 - line 32 -----	1-9, 11-12
<p>¹⁰ Special categories of cited documents : ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
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Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
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GB-A-1516348	05-07-78	AU-A- 8471475	17-03-77
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WO-A-9004963	17-05-90	EP-A- 0442949	28-08-91
		GB-A- 2243778	13-11-91
		JP-T- 4502910	28-05-92
EP-A-0486959	27-05-92	None	